Update on the current use of hormonals as therapy in advanced breast cancer

Charles L. Vogel[a]

Hormonal agents have a confirmed role in the management of postmenopausal women with receptor-positive advanced breast cancer. Until recently, tamoxifen has been the accepted agent for treating these patients. However, accumulating evidence suggests that the new antiaromatase agents will replace the antiestrogens as the preferable option in hormone-naive patients. Comparative trials indicate that the aromatase inhibitors, anastrozole and letrozole, and the aromatase inactivator, exemestane, have at least equivalent efficacy to tamoxifen with similar or superior tolerability. These agents are also more effective than the progestin, megestrol acetate, when studied in patients progressing on tamoxifen. The improved aromatase selectivity and high potency of these antiaromatase agents when compared with earlier agents have resulted in improved efficacy and tolerability. Additionally, no cross-resistance has been reported between the antiaromatase agents and tamoxifen or, in some instances, among the antiaromatase agents themselves. The role of antiaromatase agents will certainly expand in the near future to include not only treatment of metastatic breast cancer, but use in the adjuvant and neoadjuvant settings as well, and, ultimately, breast cancer prevention. The results of ongoing investigations are awaited with interest. *Anti-Cancer Drugs* 14:265–273

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[a]Cancer Research Network, Plantation, FL, USA.

Correspondence to C.L. Vogel, 350 NW 84th Avenue, Suite 300, Plantation, FL 33324, USA.
Tel: +1 954 473-6776; fax: +1 954 473-4552;
e-mail: drcvogel@aol.com

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Use of hormonal therapy in breast cancer

Estrogens, particularly estradiol, are implicated in both the initiation and promotion of breast tumors [1]. Breast cancer has been shown to be estrogen sensitive as determined by hormone receptor assays in greater than 60% of affected individuals and approximately two-thirds of these estrogen-sensitive tumors will respond to endocrine therapy [2–6]. Approximately 5–10% of patients classified as being estrogen receptor (ER)-'negative' may respond to endocrine therapy. However, many of these patients may truly be ER-positive when proper tests are used with appropriate cut-off values for positive and negative findings [2,7]. Retrospective analyses have established that, among ER-positive tumors, nearly 70% of those that are also progesterone receptor (PR)-positive and 25–30% of PR-negative tumors will respond to hormonal therapy. Additionally, concentrations of estradiol (but not estrone) are higher in malignant breast tissue than in healthy breast tissue and there is no decline in breast tissue estradiol concentrations in post-menopausal compared with pre-menopausal women despite an approximate 90% decrease in plasma estradiol concentrations [8].

Thus, the aim of hormonal treatment is to deprive the tumor of estrogenic stimulation, thus slowing disease progression [9]. After menopause or oophorectomy, the main source of androgens is the adrenal cortex. These androgens are then aromatized to estrogens and, in post–menopausal women, this latter process occurs predominantly in peripheral tissues such as adipose tissue [9,10]. In addition, breast tissue itself has been shown to be capable of estrogen biosynthesis [1].

There is no known feedback mechanism to oppose estrogen biosynthesis by peripheral tissue. Blockade of estrogen action is more likely to be achieved in post-menopausal women by the use of systemic treatment rather than removal of the ovaries, which are the main source of estrogens in pre-menopausal women [9,10]. Although the removal of the adrenal and pituitary glands had been done as a hormonal intervention three decades ago, these maneuvers are now largely of historical interest. Currently, two main pharmacological mechanisms of interfering with estrogenic activity are used. Estrogens can be prevented from interacting with cancer cells by blockade of ERs with antiestrogens. Alternatively, the biosynthesis of estrogens can be inhibited by use of antiaromatase agents [1]. Resistance to these mechanisms develops at some stage in most patients [10], so it is of some importance that cross-resistance between, and in some instances within, these two approaches has not been reported [11,12]. Hormonal agents are generally better tolerated than cytotoxic chemotherapy and may

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receive better acceptance by patients, particularly those requiring palliative treatment for advanced disease.

Targeting ERs

Tamoxifen is a selective ER modulator (SERM) that has estrogen-like effects on a number of tissues. The success of this agent in inducing antitumor responses provided evidence that antagonizing the effects of estrogen has beneficial effects in patients with breast cancer.

Tamoxifen is currently the most established hormonal treatment for women with any stage of breast cancer. It is widely used as first-line endocrine therapy in those with metastatic disease and in the adjuvant treatment of early breast cancer in women with receptor-positive tumors (regardless of age). In the adjuvant setting, tamoxifen reduces the risk of both recurrence and death when administered to patients with ER-positive tumors, but does not significantly influence disease-free or overall survival in those with ER-poor tumors. The benefits of tamoxifen in patients with receptor-positive tumors are significant, irrespective of age and menopausal status [13,14]. When given as adjuvant therapy, tamoxifen is also associated with a 39% reduction in the incidence of contralateral breast cancer [13]. This latter finding led to investigation of its value for the prevention of breast cancer and the finding that the drug reduces the risk of ER-positive tumors in women at high risk of breast cancer [15].

SERMs, because they are partial agonists, inhibit estrogenic effects in breast tumor tissue and may have beneficial effects on bone and lipid metabolism (preventing and possibly treating osteoporosis and cardiovascular disease); however, they also have potentially detrimental effects on endometrial tissue (possibly endometrial cancer) as well as being associated with thromboembolism. New SERMs have been developed to more selectively act on breast tumor tissue, and these include the orally active agents toremifene and raloxifene. Like tamoxifen, these are non-steroidal estrogen analogs that act by binding to estrogen-binding sites on the ER [16]. Tamoxifen acts as a partial agonist by activating *trans*-activating function 1 and inhibiting the activity of *trans*-activating function 2. The newer SERMs are also partial agonists, but they generally have less agonistic and more antagonistic properties than tamoxifen, and have greater affinity for the ER than tamoxifen [16]. SERMs are most effective in patients with ER-positive tumors, but they may have also demonstrated some, albeit less, activity in receptor-negative patients [17,18], although, again, this is likely to be more a function of interpretation of hormone receptor testing.

Toremifene, the better studied of the newer antiestrogens, has similar efficacy to tamoxifen in post-menopausal women with ER-positive or -unknown advanced breast cancer. Objective response (complete plus partial) rates with both agents were generally about 20% (with clinical benefit rates including prolonged stable disease approaching 50%). The duration of response, time to disease progression and median overall survival time did not differ between treatments in most clinical trials [19–22]. Both SERMs are similarly tolerated, although there is some suggestive evidence that the tolerability of toremifene is superior [19]. Evidence supporting the use of raloxifene in the treatment of breast cancer is currently limited to two small trials [23]. Most studies of this SERM have focused on its efficacy in post-menopausal women with osteoporosis, an indication for which it has been marketed [24]. However, it is being evaluated as part of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene for the Prevention of Breast Cancer (NSABP STAR) trial as a potential agent for the prevention of breast cancer [25]. Another SERM, fulvestrant, which may also be classified as a selective ER down-regulator (SERD), is now clinically available. It is highly active, administered as an intramuscular injection once a month and is essentially free of estrogen agonist properties [26]. In a combined analysis of two phase III trials, fulvestrant was found to be at least as effective as anastrozole in the treatment of post-menopausal women with advanced breast cancer whose disease progressed on endocrine therapy [27]. Where this drug will fit in the hormone therapy cascade for post-menopausal patients remains to be determined.

Targeting the aromatase enzyme

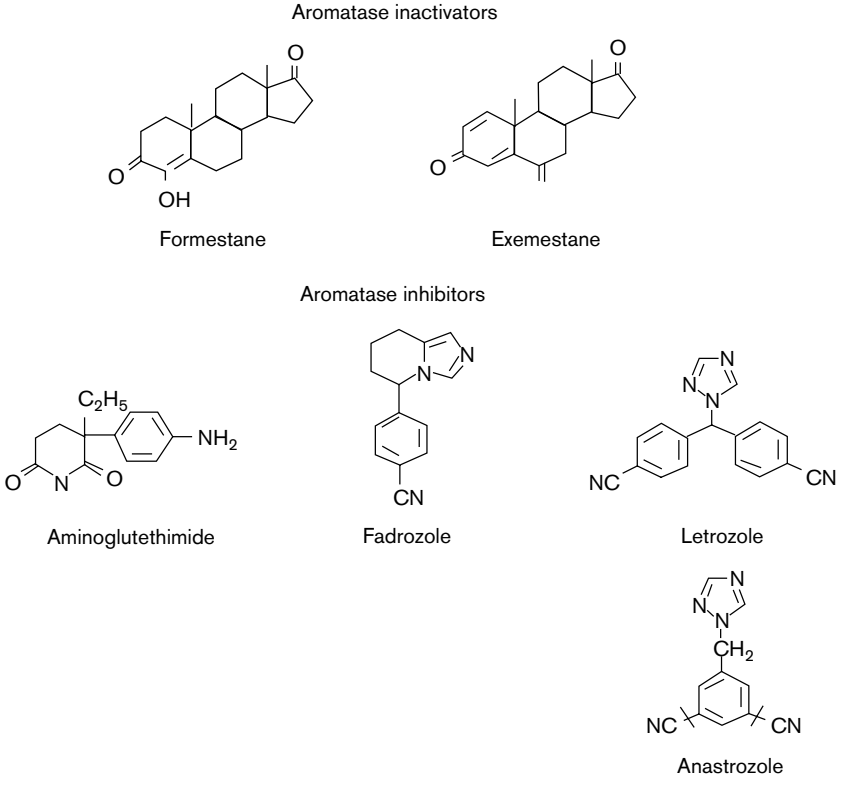
In post-menopausal women, aromatase is found predominantly in peripheral tissue (fat, the adrenal glands, muscle and skin) and also in breast tumor tissues. Indeed, aromatase expressed in breast tumor cells may have a direct effect on tumor proliferation by producing locally acting estrogens. In pre-menopausal women, most estrogen biosynthesis occurs in the ovaries, hence antiaromatase agents targeted against the small amounts of estrogens produced post–menopausally are likely to be much less effective in pre-menopausal women. Currently, there is no indication to administer an aromatase inhibitor as a single agent to pre-menopausal women. Aromatase is a membrane-bound microsomal complex comprised of two components: aromatase cytochrome P-450 (a hemoprotein responsible for catalyzing the conversion of androgens to estrogens) and a ubiquitous flavoprotein (a reductase) [9,10,12,28]. As antiaromatase agents have no estrogenic effects, they are not associated with a number of the adverse events that can occur with SERMs (e.g. endometrial effects). In addition, the incidence of menopausal symptoms (i.e. hot flashes and sweats) may be lower with the aromatase inactivator, exemestane, which is, in all probability, due to its small amount of intrinsic androgenic activity [29,30]. Another reason why

blocking estrogen synthesis may be a better choice for breast cancer prevention than blocking receptors in post-menopausal women is that estrogens can be metabolized to catecholamines and then to genotoxic quinones that may promote tumorigenesis [12]. In addition, selective blockade of estrogen synthesis with antiaromatase agents is unlikely to affect the biosynthesis of other steroids, as aromatization of androgens to estrogen is the last step in the steroidogenesis pathway [10,12].

Antiaromatase agents have been investigated and used in post-menopausal women with ER-positive or -unknown breast cancer. Along with megestrol acetate (a progestin), these agents have traditionally been used as second-line therapies after patients have received treatment with tamoxifen. Two types of antiaromatase agents are currently available: reversible competitive inhibitors (type II) (e.g. anastrazole and letrozole) and inactivators or suicide inhibitors (type I) (Fig. 1). These latter agents, which include exemestane, exhibit a high specificity for the aromatase enzyme and have long-lasting effects *in vivo*, as they bind very tightly or irreversibly to the enzyme, which remains inactivated after the free inhibitor has been cleared from the plasma. Enzyme activity is recovered only by *de novo* synthesis of aromatase. All aromatase inactivators are steroidal, whereas reversible inhibitors can be either steroidal or non-steroidal [9,10,12]. All the currently available aromatase inhibitors are orally active non-steroidal triazole analogs that noncompetitively and selectively inhibit the enzyme [31].

Aminoglutethimide was the first antiaromatase agent developed and marketed for patients with breast cancer; it is a reversible inhibitor. Unfortunately, it has several limitations, including a lack of specificity for aromatase, which leads to relatively poor tolerability. Nevertheless, aminoglutethimide, when combined with hydrocortisone, produced durable objective clinical responses in 30–50% of patients with breast cancer and had similar efficacy to, although poorer tolerability than, tamoxifen in comparative trials [32–35]. Formestane was the first selective aromatase inactivator marketed and is 60 times more potent than aminoglutethimide. Although most trials of formestane were conducted in patients (ER-positive or -unknown) who had relapsed on alternative hormonal therapies, response rates of 25–39% were reported and the drug demonstrated efficacy as first-line therapy similar to that of tamoxifen in clinical comparisons. Formestane was very well tolerated; however,

Fig. 1



Structural formulae of currently available antiaromatase agents.

intramuscular administration has led to an unfavorable acceptance [9,10]. Formestane is not commercially available in the US.

Subsequently, a number of third-generation antiaromatase agents have been developed. These are orally active, potent and highly selective for the aromatase enzyme, and include exemestane, letrozole, anastrozole and fadrozole [9,10,12,36]. As fadrozole is available only in Japan, it is not further discussed.

Antiaromatase agents in the treatment of breast cancer

Most clinical studies of antiaromatase agents have included post-menopausal women who had been previously treated with tamoxifen. However, these agents have increasingly been investigated for use as first-line endocrine therapy in post-menopausal women. The newer antiaromatase agents are highly potent and selective, and, therefore, have antitumor efficacy at relatively low daily dosages and are well tolerated [31].

The major findings for aromatase inhibitors and inactivators when used after tamoxifen are summarized in Table 1. Results of randomized comparative trials in post-menopausal women with advanced breast cancer indicate that in comparison with megestrol acetate 160 mg/day:

Anastrozole 1 mg/day produced similar response rates and appeared better tolerated. Pooled results of the two identically designed trials indicated an overall response rate [ORR, complete response (CR) + partial response (PR) + stable disease ≥ 6 months] of 42.2% with anastrozole and 40.3% with megestrol acetate. A survival advantage was demonstrated with anastrozole: the 2-year survival rate was 56.1 versus 46.3%, giving a hazard ratio of 0.78 for anastrozole ($p < 0.025$) [37].

Letrozole 2.5 mg/day produced a superior ORR (risk ratio of 0.42, $p = 0.02$), duration of response (not reached versus 17.9 months, $p = 0.02$) and time to treatment failure (TTF) (5.1 versus 3.9 months, $p = 0.04$), and was better tolerated. However, no significant between-treatment difference was demonstrated in overall survival (770 versus 655 days) [38]. Interestingly, Buzdar *et al.* [39] found that the letrozole 0.5 mg-treated group achieved a longer median time to tumor progression (TTP), TTF and time to death than the patients treated with letrozole 2.5 mg. Although the manufacturer recommends letrozole 2.5 mg/day, the inconsistencies between the studies may warrant concern about the appropriate dose.

Exemestane 25 mg/day produced a similar ORR (15 versus 12.4%) and was well tolerated. However, a survival advantage (not reached versus 123.4 weeks, $p = 0.039$), as well as significantly longer TTP (20.3 versus 16.6 weeks, $p = 0.037$) and TTF (16.3 versus 15.7 weeks, $p = 0.042$), was demonstrated with exemestane. Thus, patients given this aromatase inactivator had about a 20% lower risk of progressive disease, treatment failure or death than patients given megestrol acetate ($p < 0.05$ for all three risks) [40]. Exemestane also appeared efficacious in patients with visceral disease. This observation has led to the design of an ongoing phase III trial of exemestane versus anastrozole in patients with visceral disease.

Preliminary cost-effectiveness calculations also suggest a favorable cost-effectiveness ratio for the antiaromatase agents [41]. Further, the antiaromatase agents are not associated with the troubling side effect of weight gain, which is viewed by most women as a negative quality of life issue with progestins. Thus, available data indicate that these agents are a better option than megestrol acetate in women with advanced breast cancer who have relapsed after treatment with tamoxifen.

Antiaromatase agents in the first-line treatment of breast cancer

The promising results obtained in trials of antiaromatase agents in patients who have failed prior therapy with an antiestrogen have led to their investigation as first-line agents for the treatment of post-menopausal women with advanced breast cancer. Clinical trials evaluating the use of antiaromatase agents as first-line treatment are summarized in Table 2.

Antiaromatase agents compared with tamoxifen as first-line treatment of breast cancer

All of the trials in post-menopausal women with advanced breast cancer evaluating antiaromatase inhibitors as first-line agents included tamoxifen as a comparator are summarized in Table 2. The majority of patients involved were hormone-naive; however, a large percentage of the patient population from North America had been treated with adjuvant tamoxifen. With the exception of formestane, which is administered intramuscularly, all the antiaromatase agents have been compared with tamoxifen and have shown at least similar efficacy to the antiestrogen. Formestane produced similar response rates and had a comparable tolerability profile to that of tamoxifen; however, the median TTP and TTF were significantly longer with tamoxifen than formestane [42].

Two trials have compared anastrozole with tamoxifen. In the larger of these, all end points evaluated showed similar efficacy for the two drugs, but the smaller trial showed a significant advantage for anastrozole in terms of TTP and a tendency for higher response rates with the aromatase inhibitor (Table 2). In both trials, anastrozole appeared better tolerated than tamoxifen, particularly in terms of thromboembolic events and vaginal bleeding.

Table 1 Large trials of approved doses of antiaromatase agents as second-, third-, fourth- or fifth-line therapy in postmenopausal women with breast cancer

Reference	Previous treatment	Treatment mg/day (no. patients evaluated)	Response rate (%)			Median time (weeks)		
			CR + PR (% CR)	SD		DOR	TTP	ST
				≥ 6 months	≤ 6 months			
Exemestane								
Jones (1999) [61]	tamoxifen and MA	EXE 25 (91)	13 (4)	17	10	36	8	104
Jones (1998) [62]	tamoxifen and MA	EXE 25 (87)	11 (1)	17	not reported	96	not reported	not reported
Jones (1998) [63]	tamoxifen	EXE 25 (128)	28 (1)	19	not reported	74	not reported	not reported
Kaufmann (2000) [64]	tamoxifen	EXE 25 (366)	15 (2)	21	3	76	20[b]	NR[b]
		MA 160 (403)	12 (1)	21	3	71	17	123
Kvinnsland (2000) [65]	tamoxifen	EXE 25 (137)	23 (3)	24	0	69	25	not reported
Lonning (2000) [66]	one to four previous hormonal therapies including antiaromatase agents	EXE 25 (241)	7 (1)	17	1	58	15	NR
Anastrozole								
Buzdar (1997) [67]	tamoxifen	ANA 1 (128)	10 (3)	27	15	–[c]	24	not reported
		MA 160 (128)	6 (2)	30	13	–[c]	22	not reported
Jonat (1996) [68]	tamoxifen	ANA 1 (135)	11 (2)	24	7	37[a]	19	107 (Buzdar et al. [28])
		MA 160 (125)	10 (2)	22	11	37[a]	17	90 (Buzdar et al. [28])
Letrozole								
Dombernowsky (1998) [38]	antiestrogen therapy	LET 2.5 (174)	24b (7)	35	not reported	NR[b]	22	110
		MA 160 (189)	16 (4)	32	not reported	72	22	95
Gershanovich (1998) [69]	antiestrogen therapy	LET 2.5 (185)	20 (5)	not reported	not reported	96	14[d]	112[d]
		AMINO 500 + corticosteroids (178)	12 (1)	not reported	not reported	60	13	80
Buzdar (2001) [39]	antiestrogen therapy	LET 0.5 (202)	21 (4)	12	12	92	24	132
		LET 2.5 (199)	16 (5)	11	14	100	12	116
		MA 160 (201)	15 (2)	9	15	120	12	104

AMINO = aminoglutethimide; ANA = anastrozole; CR = complete response; DOR = duration of objective response; EXE = exemestane; LET = letrozole; MA = megestrol acetate; NR = not reached; OR = objective response, CR + PR; PR = partial response; SD = stable disease; ST = survival time; TTP = time to progression.

[a]Time to treatment failure.

[b]$p < 0.05$ versus MA.

[c]Ranged from 12 to 66 weeks, number of patients who had an OR in each treatment group was too small to provide a meaningful duration of response.

[d]$p < 0.01$ versus AMINO.

Table 2 Randomized trials of antiaromatase agents as first-line therapy in postmenopausal women with breast cancer

Reference	Treatment mg/day (no. patients evaluated)	Response rate (%)			Median time (months)		
		OR (% CR)	SD		DOR	TTP	TTF
			≥ 6 months	<6 months			
Exemestane							
Dirix (2001) [48]/Paridaens (2000) [47]	EXE 25 (60)[a]	45	11	not reported	not reported	not analyzed	not analyzed
	TAM 20 (57)[a]	14	25	not reported	not reported	not analyzed	not analyzed
Anastrozole							
Bonneterre (2000) [43]	ANA 1 (340)	33 (6)	23	3	16	8	6
	TAM 20 (328)	33 (5)	23	2	17	8	6
Nabholtz (2000) [44]	ANA 1 (171)	21 (3)	38	4	16	11[b]	8
	TAM 20 (182)	17 (3)	29	2	18	6	5
Letrozole							
Mouridsen (2001) [46]	LET 2.5 (453)	30[c] (8)	49	not reported	26	9[c]	10[b]
	TAM 20 (454)	20 (3)	38	not reported	25	6	6
Formestane							
Perez Carrion (1994) [42]	FOR 250 mg once every 2 weeks (173)	33 (8)	31 (duration not noted)	not reported	16	8	7
	TAM 30 (175)	37 (6)	34 (duration not noted)	not reported	22	1[d]	1[d]

FOR = intramuscular formestane; TAM = tamoxifen; TTF = time to treatment failure. See Table 1.
[a]Estimated: using numbers evaluable for toxicity. Numbers evaluable for response not available.
[b]$p = 0.005$ versus TAM.
[c]$p \leq 0.0006$ versus TAM.
[d]$p < 0.01$ versus formestane.

Survival was not reported for either trial [43,44]. The TTP for all patients in the combined analysis was 8.5 months for anastrozole-treated patients and 7.0 months for patients receiving tamoxifen; however, when only those patients with confirmed receptor-positive breast cancer were considered, the pooled analysis indicated a significant advantage for anastrozole over tamoxifen for TTP (10.7 versus 6.4 months, $p = 0.022$) [45]. However, there was no increase in TTP for the confirmed receptor-positive patients receiving tamoxifen compared to all tamoxifen-treated patients (including receptor unknown patients).

Letrozole has also been compared with tamoxifen in a large randomized trial. Again, follow-up time was inadequate for survival data to be reported. However, letrozole therapy was associated with a significant improvement over tamoxifen in terms of ORR, clinical benefit (objective response plus stable disease for ≥ 6 months: 49 versus 38%, $p = 0.001$), TTP and TTF (Table 2) [46].

Results of the phase II/III trial being conducted by the European Organization for the Research and Treatment of Cancer comparing exemestane with tamoxifen remain preliminary at this stage. The interim report indicates that exemestane is at least as effective as tamoxifen as first-line therapy and may be better tolerated [47,48]. Exemestane-treated patients achieved an ORR of 45% (5 CRs + 20 PRs) compared to 14% (1 CR + 7 PRs) in patients receiving tamoxifen. Positive results have led to an extended phase III trial. Exemestane is currently being compared with tamoxifen as adjuvant therapy in two studies, both of which are planned to enroll more than 3000 patients [49].

Although not a randomized trial, letrozole has been compared to tamoxifen as a neoadjuvant therapy in women with locally advanced, large, operable breast tumors. Two groups of women with similarly staged, ER-positive tumors received letrozole ($n = 24$) or tamoxifen ($n = 65$) over 3 months and were monitored by monthly ultrasound. Change in tumor volume was calculated. The median reduction in tumor volume was 81% in the patients receiving letrozole while patients in the tamoxifen group had a median reduction in tumor volume of 48%. Of note, 15 patients in the letrozole group would have required mastectomy prior to treatment. All were suitable for breast-conserving surgery after the 3-month treatment period [50]. This led to a large, phase III trial reported by Eiermann *et al.* [51]confirming superiority of letrozole over tamoxifen. In a recent subset analysis of this trial [52], this benefit was even more striking in patients with ERB-1- and ERB-2-positive tumors. To confirm or refute this critically important observation, all other phase III trials of the antiaromatase agents versus tamoxifen should be reanalyzed to determine if this observation is letrozole-specific or if shared by all the other antiaromatase agents as well. This recommendation has also been made by Pritchard [53] in her recent editorial.

Anastrozole has been evaluated as neoadjuvant therapy in 23 women with newly diagnosed, ER-positive, large or

locally advanced operable breast cancer [54]. Tumor volumes were measured at baseline and at the end of the 3-month treatment period. Results show an 80.5% decrease in tumor volume in patients taking 1 mg of anastrozole daily. Out of the 17 patients who would have required a mastectomy, 15 were suitable for breast conservation surgery after treatment.

A phase IIb trial examined neoadjuvant exemestane in 13 post-menopausal women with locally advanced breast cancer [55]. Patients received exemestane 25 mg daily for up to 3 months at which time surgery was performed. Prior to treatment with exemestane, 10 patients would have required mastectomy. At the conclusion of treatment, only two patients required mastectomy with the others able to have breast conservation surgery. The median reduction in clinical tumor volume was 85.5%. These results suggest that exemestane also is associated with a meaningful response in the neoadjuvant setting.

To date there has only been one reported trial comparing antiaromatase treatments. Rose *et al.* [56] reported an 'advantage' in response rate for letrozole versus anastrazole in patients failing tamoxifen. Interpretation of this study has been widely criticized since only half of the patients were known to be ER-positive and there were no significant differences in the primary end point (TTP) or in TTF, or in clinical benefit rate. Most importantly there was no difference in response rate among ER-positive patients.

Future perspectives

The majority of clinical data collected to date for the antiaromatase agents have involved their use as second- or third-line agents; however, evidence is rapidly accumulating regarding their efficacy as first-line agents. To date, all available phase III trials point to their superiority over tamoxifen as first-line therapy. Further studies are under way evaluating the role of these agents, alone or in combination with other established or investigational agents, in the treatment of breast cancer. Studies are also under way to establish the comparative efficacies of the aromatase inhibitors and aromatase inactivators. Thus, trials comparing exemestane, which is the only orally active inactivator, with anastrozole and letrozole will help to clarify the optimal role of these agents in patients with breast cancer.

Of critical importance before the true value of the new antiaromatase agents can be exploited, is to establish the potential of these agents in the treatment of post-menopausal women with early disease, particularly in the adjuvant and neoadjuvant settings (Table 3). Indeed, the first large-scale adjuvant trial of an aromatase inhibitor shows superiority of anastrazole over both tamoxifen and the combination although follow-up in this trial is still less than 5 years, the 47-month follow-up of the ATAC trial confirms a 2.9% benefit of single agent anastrazole in disease-free survival. Most safety parameters except for fractures and musculoskeletal disorders also favor anastrozole [57,58].

Investigations into the use of each of these agents in cancer prevention are planned. The effects these agents have on bone density and lipids are also being evaluated. Exemestane has reported positive data in maintenance of bone mineral density and lowering cholesterol [59], while letrozole has documented a significant effect on bone resorption [60]. Data are currently unavailable for anastrozole.

Conclusions

The role of antiaromatase agents as second-line therapy has been established and they have shown increasing potential as first-line therapy in the treatment of hormone-receptor positive breast cancer in post-menopausal women. All three orally active antiaromatase agents (anastrozole, letrozole and exemestane) are highly active and comparative trials will be needed to establish superiority or equivalence of one versus the others. Such comparative trials might also determine whether exemestane, the only steroidal orally active aromatase inactivator, with its irreversible aromatase binding and

Table 3 Current clinical trials involving antiaromatase agents.

Title	Agent(s) used	Projected total accrual	No. of arms
Adjuvant Tamoxifen or Arimidex or Combined (ATAC)	tamoxifen (5 years), anastrozole (5 years) or both (5 years)	~9000	3
Breast International Group (BIGFEMTA)	letrozole (5 years), tamoxifen (2 years) → letrozole (3 years), letrozole (2 years) → tamoxifen (5 years) or letrozole (5 years)	~4000	4
BIG031	tamoxifen (2–3 years) → tamoxifen (2–3 years) or exemestane (2–3 years)	~4400	2
MA17	tamoxifen (5 years) → letrozole (5 years) or placebo	~4800	2
National Surgical Adjuvant Breast and Bowel Project (NSABP B33)	tamoxifen (5 years) → exemestane (2 years) or placebo	~3000	2
International Collaborative Cancer Group (ICCG-Trial)	tamoxifen (3 years) → exemestane (2 years) or tamoxifen (2 years)	~4400	2
ARNO	tamoxifen (2 years) → anastrozole (3 years) or tamoxifen (3 years)	?	2

favorable tolerability profile, has clinical advantages over the non-steroidal inhibitors. Having at least equivalent efficacy to tamoxifen and similar or superior tolerability, it is likely that the antiaromatase agents will replace tamoxifen early in the millennium as first-line therapy of post-menopausal women with advanced breast cancer. These agents will most likely have significant future roles in the adjuvant, neoadjuvant and cancer prevention settings.

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